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Change in the Frequency of Diabetic Ketoacidosis in Children with Newly Diagnosed Type 1 Diabetes in the Central Anatolia Region of Turkey over the Years Before and After the Coronavirus Disease 2019 Pandemic: A Single-Center Experience

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What is already known on this topic?

- *There are many study reports showing that the frequency of ketoacidosis is higher in children with newly diagnosed type 1 diabetes during the pandemic period.*
- *Studies have also reported that this effect may be due to lockdown, disruptions in healthcare, or the direct effect of coronavirus disease 2019.*

What this study adds on this topic?

- *The frequency of diabetic ketoacidosis in children with newly-diagnosed type 1 diabetes increased in the first years of the pandemic. It has been decreasing over the years towards pre-pandemic levels.*
- *The frequency of diabetic ketoacidosis is still higher than the pre-pandemic period.*

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ABSTRACT

Objective: The number of admissions for severe diabetic ketoacidosis (DKA) in children with newly diagnosed type 1 diabetes (T1D) increased during the coronavirus disease 2019 pandemic. We aimed to investigate whether there has been a change in this situation in recent years.

Materials and Methods: All children with T1D who were diagnosed in our tertiary hospital between 2019 and 2023 were included. Plasma insulin, C-peptide, hemoglobin A1c (HbA1c), and antibodies against thyroid peroxidase, thyroglobulin, insulin, islet cell, glutamic acid decarboxylase, tissue transglutaminase IgA, and endomysium IgA were measured.

Results: The frequency of moderate–severe acidosis at admission, which increased after pandemic period compared to the pre-pandemic period, returns to its previous levels over time but still shows a statistical difference compared to the pre-pandemic period (P = .012). Age, blood gas pH and HCO_3 level, C-peptide, HbA1c, and length of stay of children at the time of admission were compared year by year (years 2019-2023). No statistical differences were observed (P = .509, P = .181, P = .069, P = .469, P = .346, P = .946), respectively. A significant difference was observed in venous glucose (P < .001) and insulin (P = .001) according to years. Also, no significant difference was found about the degree of acidosis according to age (P = .334).

Conclusion: Although the frequency of DKA in children with newly-diagnosed T1D increased in the first years of the pandemic, it has been decreasing over the years toward pre-pandemic levels. The frequency of DKA is still higher than the pre-pandemic period.

Keywords: Children, COVID-19, diabetic ketoacidosis, frequency, type 1 diabetes

INTRODUCTION

Type 1 diabetes (T1D) is an autoimmune disorder that occurs on a genetic basis, triggered by the effects of several environmental factors.[1] Some of these factors are chemically contaminated foods and viral infections. These triggers and autoimmunity lead to partial or complete destruction of the insulin-producing cells of the pancreas and, as a result, insulin deficiency occurs.[1] According to the International Diabetes Federation Atlas 2022 Reports data, it is stated that 8.75 million people have T1D worldwide.[2] The number of newly diagnosed diabetics in all age groups in 2022 is 530.000, and 201.000 of them are under the

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age of 20 years.[2] It has been reported that there is a worldwide increasing trend in the incidence of T1D in children under 15 years of age.[3] Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. After the first known case was detected in Wuhan, China, in December 2019, the disease quickly spread worldwide, resulting in the COVID-19 pandemic. Between 2020 and 2022, its impact continued with different variants in different countries from time to time, but its global impact decreased with vaccination policies, individual mask use, physical distance, hygiene precautions, and lockdown. There are many study reports showing that the frequency of ketoacidosis is higher in children with newly diagnosed T1D during the pandemic period.[4-6] Studies have also reported that this effect may be due to lockdown, disruptions in health care, or the direct effect of COVID-19.[7,8] There are also results reporting that the risk of T1D in children does not increase after SARS-CoV-2 infection.[9] In a meta-analysis, pre-pandemic and first-year data at the beginning of the pandemic were compared and it was found that median glucose and glycosylated hemoglobin A1c (HbA1c) levels increased in children with newly diagnosed T1D. In addition, in this meta-analysis, the change in incidence rates between 2019 and 2020 was compared and it was shown that the global risk of pediatric new-onset T1D, diabetic ketoacidosis (DKA), and severe DKA increased.[10,11] However, regional differences are noteworthy. It is seen that this increase is more pronounced in countries, which have a relatively high incidence of T1D.[10,12]

In this study, we examined the course of changes over the years in the clinical and biochemical findings of children with newly diagnosed T1D at the time of admission between 2019 and 2023. We aimed to see whether the seasonal or monthly distribution of diagnosis frequency and the severity and frequency of ketoacidosis at the time of admission resemble pre-pandemic periods as the global impact of the pandemic decreases.

MATERIALS AND METHODS

Study Design

This cross-sectional study was carried out in pediatric endocrinology and pediatric intensive care units of a tertiary hospital in the Central Anatolia region of Turkey. Data were collected retrospectively from the medical records of the patients. The diagnosis of T1D was considered according to the International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines 2022.[13]

All children with T1D who were diagnosed in our hospital between 2019, when the COVID-19 pandemic was announced, and the third quarter of 2023 were included in this study. Patients with negative T1D-specific antibodies at the time of admission and who did not require insulin during follow-up were excluded from the study. Among those who had negative diabetes-specific antibodies and used insulin, cases suggestive of monogenic diabetes (the number of neonatal diabetics = 3, the number of patients with maturity-onset diabetes of young = 7), cases suggestive of insulin resistance, and cases suggestive of type 2 diabetes (n = 6), were not included in this study.

Laboratory Measurements

Plasma insulin, C-peptide, HbA1c, antibodies against thyroid peroxidase, and thyroglobulin were measured by elect rochemiluminescence immunological method on the Cobas 8000 e602 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Helmed brand device and Aesku branded kit (Wendelsheim, Germany) were used for measurement of anti-endomysium antibody, Seac brand Alisei model device and Orgentec brand kit (Mainz, Germany) were used for measurement of tissue transglutaminase IgA, by enzyme-linked immunosorbent assays (ELISA). Insulin autoantibody was measured by radio immune assay method, islet cell antibody was measured by indirect immunofluorescence method, and glutamic acid decarboxylase antibody was measured by ELISA method.

Ethics Committee Approval

The study was approved by the Ethics Committee of Kayseri City Education and Research Hospital (Approval decision date: April 4, 2023, Number: 819) and carried out in accordance with the Declaration of Helsinki. Written informed consent form was obtained from the family or legal guardians.

Statistical Analysis

Statistical analysis of the data was evaluated using the Statistical Package for the Social Sciences version 24.0 (IBM Corporation, Armonk, NY, USA) software program. The mean, standard deviation, median, first (Q1) and third (Q3) quartiles, and minimum and maximum values of numerical variables were calculated. The numbers and percentages (%) of categorical variables were determined. Shapiro–Wilk test was used to evaluate the normal distribution of variables. In addition, the variables with kurtosis and skewness values in the range of –2 to +2 were considered to have normal distribution. Chi-square analysis and Fisher exact tests were used to compare categorical variables. In the comparison of 2 independent variables, Student's *t*-test was used if the variables were in accordance with the normal distribution, and the Mann–Whitney *U*-test was used if they did not. One-way analysis of variance test was used to compare independent variables. Homogeneity of variances was evaluated with Levene's test. Kruskal–Wallis test was used to compare groups that did not comply with normal distribution. For statistical significance, a *P*-value below .05 was accepted.

RESULTS

A total of 188 children (94 female, 94 male) under the age of 18 with new-onset T1D who applied to our center in the last 5 years were included in the study. In terms of ethnicity, 164 children were of Turkish, 21 children were of Syrian, Iraqi, and Arab origin, and most of them were immigrants who took refuge in Turkey due to the Syrian civil war. Of the remaining 3 children, 2 were of Afghan origin and 1 was of Russian origin. The number of children with T1D diagnosed in the year of the COVID-19 pandemic broke out, which started in the last months of 2019 and caused a global pandemic, was of 25 (13.3%). The number of children with T1D diagnosed in 2020, the first year of the pandemic period in Turkey, was of 6 (3.2%). One reason for this may be that our center was working only to provide COVID-19 patients services at that time, and cases other than emergency services and those negative for diagnosed with COVID-19 were referred to other hospitals. The total number of children with

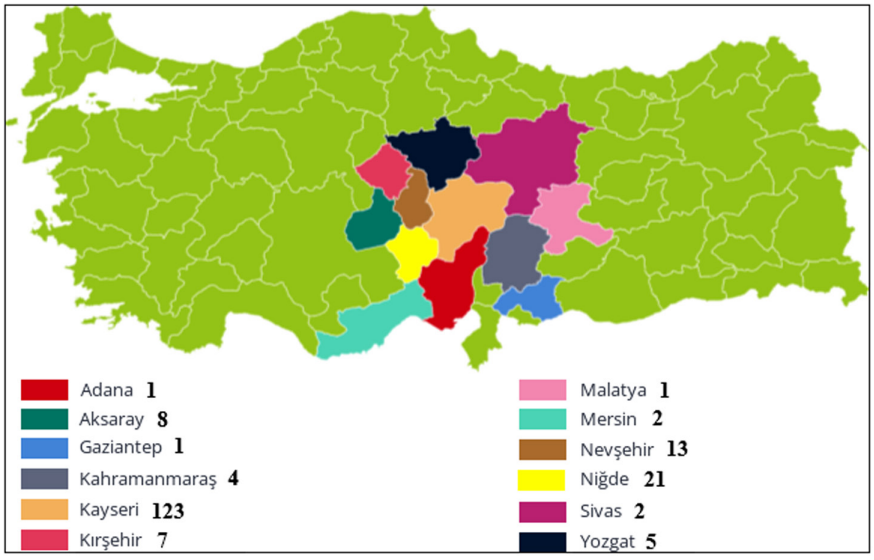

Figure 1. Distribution of cities where patient admissions come from at the time of diagnosis.

new-onset T1D in 2021, 2022, and the first 6 months of 2023 were 157 (73.5%). While the average age of the cases (n = 163) who have applied since the pandemic began was 9.4 ± 4.1 years, the average age of the cases (n = 25) diagnosed in the year before the pandemic was 9.6 ± 3.9 years, there was no statistical difference (*P* = .84).

At the time of admission, 83 (44.1%) patients had acidosis, 33 (17.6%) patients had ketosis without acidosis, and 72 (38.3%) patients had only hyperglycemia. Of the cases with acidosis, 17 (20.5%) had mild acidosis, 29 (34.9%) had moderate acidosis, and 37 (44.6%) had severe acidosis. Of these patients, 73 (38.8%) were monitored in pediatric intensive care and 115 (61.2%) were monitored in pediatric wards. While 58 (87.9%) of the children with moderate to severe acidosis (66 cases) at the time of admission could be monitored in intensive care conditions, 8 (12.1%) had to be monitored in inward conditions. When the pre-pandemic (12%) and post-pandemic admissions (38.7%) were compared, a significant difference was observed in terms of the frequency of moderate and severe acidosis, which may require intensive care (*P* = .012). The average length of stay for a hospitalization was 6.7 ± 2.5 days.

While a number of 123 (65.4%) admissions applied from the provinces and districts where our center is located, a number of 65 (34.6%) admissions were from surrounding provinces. Cities where patient admissions come from are shown in Figure 1. The distribution of admissions by the months and seasons in which the patients were diagnosed before and after the COVID-19 pandemic is shown in Figure 2.

Biochemical findings of children with newly diagnosed T1D at admission are shown in Table 1.

A comparison of the last year before the COVID-19 pandemic and the last 4 years during and after the pandemic is shown in Table 2.

Change in Ketoacidosis Admission Characteristics According to Years and Age Groups

The frequency of moderate–severe acidosis at the time of admission, which increased after the pandemic compared to the pre-pandemic, returns to its previous levels over time but still shows a statistical difference compared to the pre-pandemic period (*P* = .012). The frequency of moderate–severe acidosis in newly diagnosed T1D admissions by years over time is shown in Figure 3. In addition, the findings of children with diabetes at the time of admission, age, length of stay, blood gas pH, and HCO_3 level, venous glucose, insulin, C-peptide,

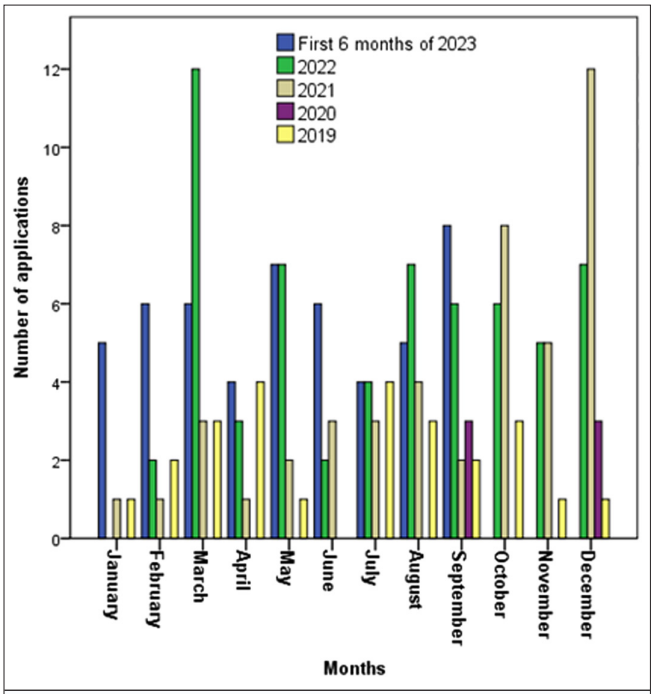

Figure 2. Distribution of admissions of type 1 diabetes by the months before and after the coronavirus disease 2019 pandemic.

Table 1. Biochemical Findings of Children with New-Onset Type 1 Diabetes at Admission

	Mean ± SD	Median (Q1-Q3)	Minimum–Maximum
Blood gas pH	7.22 ± 0.18	7.26 (7.14-7.37)	6.8-7.58
Blood gas HCO_3 (mEq/L)	15.9 ± 6.9	16.5 (10.2-22)	2.7-28.2
Venous glucose (mg/dL)	418 ± 157	379 (314-499)	147-1200
Insulin (mU/L)	3.5 ± 3.3	2.5 (1.2-4.6)	0.2-17.1
C-peptide (µg/L)	0.7 ± 0.7	0.5 (0.3-0.9)	0.02-.52
Hemoglobin A1c (%)	12.1 ± 2.2	12.2 (10.7-13.6)	5.8-18.7

and HbA1c were compared year by year (years 2019–2023). These data are shown in Table 3.

The patients were divided into 4 subgroups according to age, 0-5 years, 6-10 years, 11-15 years, and 16 years and above. In these subgroups, admissions according to the degree of acidosis (no acidosis, mild, moderate, severe acidosis) were compared age groups, and no significant difference was found (P = .334). The change in newly diagnosed T1D admission patterns over the years according to age groups is shown in Figure 4.

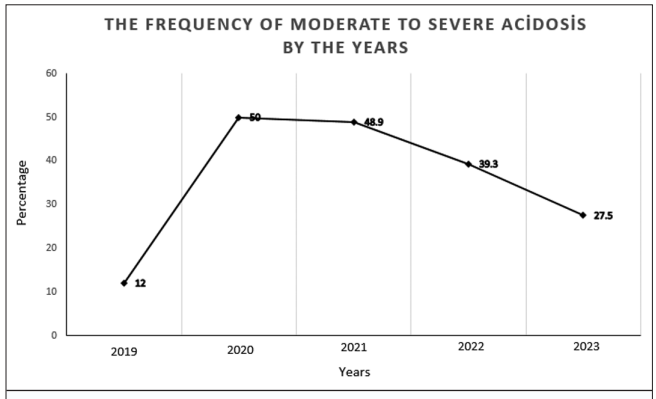

Figure 3. Frequency of moderate–severe acidosis in newly diagnosed type 1 diabetes admissions by years.

Table 2. Comparison of the Last Year Before the Coronavirus Disease 2019 Pandemic and the Last 4 Years During and After the Pandemic

	Year 2019		Year Between 2020 and 2023		*P*
Gender	14 Female/11 Male		80 Female/83 Male		.668*
Ethnicity	24 Turkish/1 Foreign		140 Turkish/23 Foreign		.210†
Hospitalization	Ward: 16 (64%) PICU: 9 (36%)		Ward: 99 (60.7%) PICU: 64 (39.3%)		.828*
	No	Yes	No	Yes	
Presence of moderate-to-severe acidosis	22 (88%)	3 (12%)	100 (61.3%)	63 (38.7%)	.012*
Presence of polydipsia	2 (8%)	23 (92%)	20 (12.7%)	138 (87.3%)	.743†
Presence of polyuria	1 (4%)	24 (96%)	18 (11.5%)	139 (88.5%)	.479†
Presence of weight loss	7 (28%)	18 (72%)	32 (26%)	91 (74%)	1.00*
Impairment of consciousness at admission	4 (16%)	21 (84%)	75 (46.6%)	86 (53.4%)	.004*
Presence of diabetes in family members	20 (80%)	5 (20%)	110 (69.6%)	48 (30.4%)	.349*
Anti-GAD Ab positivity	6 (75%)	2 (25%)	64 (40.8%)	93 (59.2%)	.072†
Anti-islet Ab positivity	5 (71.4%)	2 (28.6%)	73 (47.4%)	81 (52.6%)	.265†
Anti-insulin Ab positivity	8 (100%)	0 (0%)	144 (92.9%)	11 (7.1%)	1.00†
Presence of Hashimoto's thyroiditis at admission	17 (94.4%)	1 (5.6%)	144 (90.6%)	15 (9.4%)	1.00†
Celiac disease-specific Ab positivity at admission	15 (83.3%)	3 (16.7%)	137 (86.2%)	22 (13.8%)	.723†

Ab, antibody; GAD, glutamic acid decarboxylase antibody; PICU, pediatric intensive care unit.
αIndicates chi-square test was used.
βIndicates Fisher's exact test was used.

Table 3. Findings of Children with Diabetes at the Time of Admission Year by Year (2019-2023)

	Year 2019	Year 2020	Year 2021	Year 2022	First 6 months of 2023	*P*
Age (years)	9.6 ± 3.9	11.5 ± 3.7	10 ± 4.1	9 ± 4.3	9.1 ± 3.7	.509†
Length of stay (years)	7.1 ± 3	6.5 ± 2	6.8 ± 2.4	6.8 ± 2.6	6.6 ± 2.4	.946†
pH level	7.3 ± 0.2	7.1 ± 0.2	7.2 ± 0.2	7.2 ± 0.2	7.3 ± 0.2	.181†
HCO_3 (mEq/L)	18.1 ± 7.6	13.4 ± 7.8	14 ± 6.7	17.6 ± 5.9	15.6 ± 6.9	.069†
Venous glucose (mg/dL)	379 ± 134	571 ± 358	484 ± 146	375 ± 112	414 ± 165	<.001†
Insulin (mU/L)	4.6 (1.9-8.4)	0.2 (0.2-0.2)	3.5 (2.1-5.5)	2.2 (1.1-3.9)	1.6 (0.9-3.8)	.001*
Hemoglobin A1c (%)	11.7 ± 2.1	11.7 ± 2.3	12.5 ± 1.8	11.8 ± 2.3	12.4 ± 2.6	.346†
C-peptide (µg/L)	0.5 (0.3-1.3)	0.3 (0.3-0.3)	0.5 (0.3-0.8)	0.5 (0.3-1)	0.4 (0.2-0.8)	.303*

Variables that comply with normal distribution are presented as mean ± standard deviation, and those that do not comply with normal distribution are presented as median—first (Q1) and third (Q3) quartiles.
†One-way analysis of variance test was used to compare groups with normal distribution.
*Kruskal–Wallis test was used to compare groups that did not comply with normal distribution.

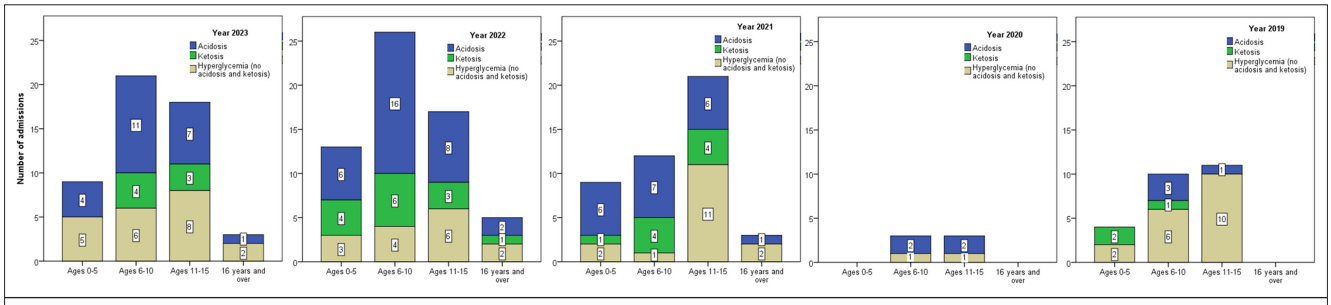

Figure 4. Change in newly diagnosed type 1 diabetes admission patterns over the years according to age.

DISCUSSION

Our study is a cross-sectional study in which the admission characteristics of children with newly diagnosed T1D between 2019 (the year the COVID-19 pandemic started) and 2023 are compared and evaluated according to years. It is the first study with the longest period to show the frequency of newly diagnosed patients with T1D admitted due to moderate and severe ketoacidosis, according to years after the COVID-19 pandemic. Although moderate–severe DKA frequency is decreasing compared to the period at the beginning of the pandemic, it is still higher than in the period before the pandemic. In addition, it was noteworthy that the impairment in the level of consciousness accompanying the classical findings (polydipsia, polyuria, weight loss) at the time of admission was more common in recent years.

While studies were reporting an increase in the incidence of T1D in the first years of the pandemic,[14] there were also studies reporting that the incidence did not change statistically compared to before the pandemic.[4] Many countries have reported an increase in the frequency of DKA in the diagnosis of T1D in recent years; in 1 study, in addition to the increasing frequency between 2006 and 2019, an additional increase was also reported in the first years of the pandemic (between 2020 and 2021).[15] In a study examining the nationwide registry (between 2011 and 2013) in Turkey, the incidence of T1D in children under the age of 18 was 10.4/100 000 in boys and 11.3/100 000 in girls. The prevalence of T1D was 0.75/1000.[16] In a study conducted in Diyarbakır in 2020, the frequency of severe DKA was found to be 26.3% in newly diagnosed T1D admissions.[17] It was stated that in the first year of the pandemic in Turkey, the frequency of cases admitted to pediatric intensive care units (27 centers) across the country due to severe DKA increased compared to the previous year (70.2% vs. 56.5%).[18] However, it is also stated that this study cannot clearly show the frequency of DKA in all newly diagnosed diabetics, as hospitalizations of wards or admissions with hyperglycemia were not evaluated.[18] In another study where the frequency of DKA was evaluated in the first year of the pandemic in Turkey compared to the previous year, the frequency of severe DKA among hyperglycemia, ketosis, and ketoacidosis admissions was found to be 23%.[19]

Studies conducted before the pandemic reported that the frequencies of DKA varied between 15% and 70% in Europe and North America, and that DKA was generally detected more frequently in countries where T1D was less common.[20]

In a study from Iran, it was reported that the frequency of severe DKA (in newly diagnosed patients with T1D) increased during the pandemic period compared to the pre-pandemic period (35.7% vs. 21.2%).[21] Studies are comparing the first months after the beginning of the pandemic with previous years and found that the frequency of DKA in newly diagnosed patients with T1D was higher than in previous years.[4,6,22] In these studies, the period of the first wave of the pandemic in 2020 was compared. During this period, reasons such as restrictions, lack of access to health-care services, and the inadequacy of hospitals in providing health-care services were cited as reasons for this increase in frequency. Unlike other studies, in a single-center study, including 370 patients from the pre-COVID period (between 2017 and 2020) and 42 patients from the post-COVID period (in 2020); including 171 girls and 241 boys, in which the frequency of DKA at the time of diagnosis was evaluated, there was no statistical difference detected when the acidosis degrees were compared (13% vs. 14% for mild DKA, 33% vs. 31% for moderate or severe DKA, respectively).[23] However, there are not enough long-term studies in the literature that evaluate the years 2020 and beyond.

As an example of regional studies in our country, in a study that examined the initial presentation of patients with T1D at a tertiary health-care institution in Malatya and included a 24-year follow-up (1996-2019) before the pandemic, it was found that the frequency of ketoacidosis decreased over time and the frequency of hyperglycemia and ketosis increased.[24] In a study examining the years 2009 to 2019 in Elazığ, it was observed that the increasing trend in the incidence of T1D was especially in boys, urban residents, and children between the ages of 5 and 9 years.[25] In another study examining newly diagnosed T1D cases in Elazığ between 2016 and 2019, it was observed that the presence of DKA at the time of diagnosis was associated with high HbA1c levels, and that presentation with severe DKA was associated with people living in rural areas and low education levels of mothers.[26] Newly diagnosed T1D cases examined in tertiary care in the Southern region of Turkey between 2019 and 2021 were compared as 2 groups before and after the pandemic, and it was found that the frequency of severe DKA was higher in cases diagnosed after the pandemic, and antibody positivity for celiac disease and glutamic acid decarboxylase were observed more common.[27] In a study reported from the Mediterranean region of our country, the authors found that the rates of DKA and severe DKA were similar, although they found an increase in the number of new-onset T1D cases in the first years of the pandemic compared to before the pandemic.[28]

Studies in the literature are generally designed to compare the first year or first 2 years of the pandemic period with

previous years, and in terms of comparison, the number of cases is generally designed to be mostly from the pre-pandemic period. In our study, we included the year 2019 before the pandemic and the years after the pandemic (from 2020 to 2023), and compared year by year. The advantage of our study compared to other studies is that the clinical and biochemical characteristics of children with newly diagnosed T1D who were admitted to the pediatric ward or pediatric intensive care unit were adequately examined. For example, admissions were classified according to the degree of ketoacidosis (mild, moderate, severe), ketosis, or isolated hyperglycemia. In addition, the changes in admission patterns after the pandemic over the years were examined according to age distribution. Although our study provides cross-sectional results, the fact that the frequency of ketoacidosis is still higher in children with newly diagnosed T1D after the pandemic compared to the pre-pandemic period shows that the impact of the pandemic on society may last for years. It has also been shown in a study conducted in our country that COVID-19 affects the psychosocial dimensions of the families of children with T1D.[29]

Our study also has some limitations. First, the pre-pandemic period was not evaluated as a long period. Second, our center provides cross-sectional results about a single center of central Anatolia and does not reflect the centers across Turkey. December 2019 was taken as the pandemic start date. Evaluations were made according to years and 2019 was taken as pre-pandemic and 2020-2023 as post-pandemic, but the first case in Turkey was seen in March 2020. Although this may seem like a limitation; we think that more clear results will be obtained as the number of studies evaluating the post-pandemic period over the years increases. Our center has started to serve as a regional city hospital since May 2018. For this reason, the years before 2019 could not be compared.

Although the frequency of DKA in children with newly-diagnosed T1D increased in the first years of the COVID-19 pandemic, it has been decreasing over the years toward pre-pandemic levels. The frequency of DKA is still higher than the pre-pandemic period.

Ethics Committee Approval: The study was approved by the Ethics Committee of Kayseri City Education and Research Hospital (Approval decision date: April 4, 2023, Number: 819).

Informed Consent: Written informed consent form was obtained from the family or legal guardians.

Peer-review: Externally peer-reviewed.

Author Contributions: Study Conception and Design – S.B.K., M.Ç., S.Ö., A.D.; Data Collection – S.B.K., M.Z.T., R.D.; Analysis and Interpretation of Results: S.B.K., M.Ç., S.Ö., A.D.; Manuscript Preparation – S.B.K.

Declaration of Interests: The authors declare that they have no conflict of interest.

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